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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Impact of Morphological Status on Long-Term Outcome Among Patients Undergoing Liver Surgery for Intrahepatic Cholangiocarcinoma

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ABSTRACT

Background. The influence of morphological status on the long-term outcome of patients undergoing liver resection for intrahepatic cholangiocarcinoma (ICC) is poorly defined. We sought to study the impact of morphological status on overall survival (OS) of patients undergoing curative-intent resection for ICC.

Methods. A total of 1083 patients who underwent liver resection for ICC between 1990 and 2015 were identified. Data on clinicopathological characteristics, operative details, and morphological status were recorded and analyzed. A propensity score-matched analysis was performed to reduce confounding biases.

Results. Among 1083 patients, 941(86.9%) had a mass-forming (MF) or intraductal-growth (IG) type, while 142 (13.1%) had a periductal-infiltrating (PI) or MF with PI components (MF + PI) ICC. Patients with an MF/IG ICC had a 5-year OS of 41.8% (95% confidence interval [CI] 37.7–45.9) compared with 25.5% (95% CI 17.3–34.4) for patients with a PI/MF + PI ($p < 0.001$). Morphological type was found to be an independent predictor of OS as patients with a PI/MF + PI ICC had a higher hazard of death (hazard ratio [HR] 1.42, 95% CI 1.11–1.82; $p = 0.006$) compared with patients who had an MF/IG ICC. Compared with T1a–T1b–T2 MF/IG tumors, T1a–T1b–T2 PI/MF + PI and T3–T4 PI/MF + PI tumors were associated with an increased risk of death (HR 1.47 vs. 3.59). Conversely, patients with T3–T4 MF/IG tumors had a similar risk of death compared with T1a–T1b–T2 MF/IG patients ($p = 0.95$).

Fabio Bagante and Gaya Spolverato contributed equally to this article.

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Conclusion. Among patients undergoing curative-intent resection of ICC, morphological status was a predictor of long-term outcome. Patients with PI or MF + PI ICC had an approximately 45% increased risk of death long-term compared with patients who had an MF or IG ICC.

Intrahepatic cholangiocarcinoma (ICC) is a primary liver tumor that originates from the endothelial cells of segmental or proximal branches of the bile duct.[1] It accounts for 10–15% of all primary liver malignancies and its incidence and mortality are increasing worldwide.[2] Surgical resection remains the cornerstone of potentially curative therapy, however 5-year survival after curative-intent resection remains only 25–30%.[2–11] Several studies have identified clinicopathological factors associated with long-term outcomes.[2,7,9,12–18] Specifically, preoperative cancer antigen (CA) 19–9 levels, tumor number and size, lymph node status, margin status, and vascular invasion have each been associated with an increased risk of death long-term.[2,7,9,12–17,19]

Another less-considered clinicopathological characteristic of ICC involves tumor morphology. The Liver Cancer Study Group of Japan has classified ICC into several categories based on gross appearance: mass-forming (MF) type, periductal-infiltrating (PI) type, and intraductal-growth (IG) type. The MF type is characterized by a defined mass within the liver parenchyma, while the PI subtype extends longitudinally along the bile duct, often with enhancement of the bile duct. In contrast, the IG type grows toward or within the lumen of the bile duct.[20] While these different ICC morphologies have been defined, few studies have investigated the impact of tumor morphology on long-term prognosis following resection of ICC.[21–23] Shimada et al. reported that MF + PI ICC had a higher incidence of positive surgical margins, as well as a higher risk of local recurrence.[21] However, previous studies have been limited due to small patient cohorts derived from single institutions.

Given the lack of data, the objective of the current study was to define the impact of ICC morphologic status relative to long-term outcomes following liver resection for ICC using a large multi-institutional international cohort. In addition, we sought to define the relationship of tumor morphology and the American Joint Committee on Cancer (AJCC) 8th edition T categories.

INTRODUCTION

PATIENTS AND METHODS

Study Population and Data Collection

Patients who underwent hepatic resection for histologically confirmed ICC at one of 14 major hepatobiliary centers between 1990 and 2015 were identified. The 14 medical centers included Johns Hopkins Hospital, Baltimore, MD, USA; Stanford University, Stanford, CA, USA; University of Virginia, Charlottesville, VA, USA; Emory University, Atlanta, GA, USA; Fundeni Clinical Institute of Digestive Disease, Bucharest, Romania; Curry Cabral Hospital, Lisbon, Portugal; Ospedale San Raffaele, Milan, Italy; Royal Prince Alfred Hospital, University of Sydney, Sydney, NSW, Australia; Eastern Hepatobiliary Surgery Hospital, Shanghai, China; Beaujon Hospital, Clichy, France; University of Ottawa, Ottawa, ON, Canada; Erasmus University Medical Centre, Rotterdam, The Netherlands; Yokohama City University School of Medicine, Yokohama, Japan; and University of Verona, School of Medicine, Verona, Italy. The Institutional Review Board of the participating institutions approved the study. Only patients who underwent curative-intent liver resection for nonmetastatic tumors were included. Patients who underwent a noncurative resection (R2), as well as patients who received only ablation or intra-arterial therapy, were excluded.

Standard patient demographic and clinicopathological characteristics were collected, including age, sex, American Society of Anesthesiologists (ASA) class, presence of cirrhosis in the underlying liver, and serum level of carcinoembryonic antigen (CEA) and CA19-9. ICC-specific characteristics, including tumor location, tumor burden, invasion of adjacent organs, liver capsule involvement, margin status, tumor grade, major vascular/lymphovascular/perineural invasion, and nodal status were collected. For the purposes of analyses, patients were grouped as MF/IG type versus PI/MF with PI components (MF + PI) ICC. For all cases, the imaging and pathological data were reviewed to determine the macroscopic morphologic subtype. In addition, since early 2000, ICC morphological type has been included in the pathological report as a standard data field regarding tumor characteristics at the 14 participating centers. Treatment-related data such as type and extent of hepatic resection, lymphadenectomy, and receipt of neoadjuvant chemotherapy were also recorded. Tumor stage was categorized according to the 8th edition of the AJCC.[24] The presence of multifocal ICC, invasion of adjacent organs, liver capsule involvement, margin status, tumor grade, vascular/lymphovascular/perineural invasion, nodal status, morphological type, and AJCC stage were determined based on final pathological reports.

Statistical Analysis

Discrete variables were described as medians with interquartile range (IQR) and categorical variables were recorded as totals and frequencies. Univariable comparisons were assessed using the Chi square test or Fisher's

exact test as appropriate. Univariable and multivariable analyses were performed using Cox proportional hazard regression models to assess possible associations among covariates. Variables significant on univariable analysis ($p < 0.05$) were entered into the multivariable model and backward selection was used to eliminate nonsignificant variables at $p < 0.10$. Furthermore, to account for any potential residual confounders in the effect of morphologic subtype classification on survival, propensity scores were estimated using a logistic regression model, with morphological type specified as MF/IG versus PI/MF + PI. Age, ASA score, underlying liver disease, neoadjuvant chemotherapy, type of surgery, margin status, liver capsule involvement, invasion of adjacent organs, tumor size and number, tumor differentiation, major vascular invasion, lymphovascular invasion, perineural invasion, lymph node status, and AJCC 8th edition T-staging system were included as independent variables in the logistic regression model. For matching, a caliper width of 0.1 times the standard deviation of the propensity score was used. The degrees of covariate imbalance in unmatched and matched samples were measured using the standardized (mean and proportion) differences as proposed by Austin et al.[25] A p value <0.05 (two-tailed) was considered statistically significant. All analyses were performed using STATA version 12.0 (StataCorp LP, College Station, TX, USA) or R software for statistical computing, v. 3.0.2 34, with the additional packages, survival, Hmisc and Matching.

RESULTS

Baseline Characteristics of the Study Group Stratified by the Intrahepatic Cholangiocarcinoma Morphological Types

Among 1083 patients who underwent liver resection for ICC, 911 (84.1%) patients had a MF type ICC, 30 (2.8%) had an IG type, 54 (5.0%) had a PI type, and 88 (8.1%) patients had an MF + PI type ICC. Accordingly, 941 (86.9%) patients were included in the MF/IG group, while 142 (13.1%) were included in the PI/MF + PI group (Table 1). While most clinical characteristics were comparable in the two groups, patients with MF/IG ICC were younger than patients with PI/MF + PI ICC tumors (MF/IG 59 years vs. PI/MF + PI 63 years; $p = 0.008$) and had a lower ASA score (ASA score >2, MF/IG: 53.5% vs. PI/MF + PI: 41.8%; $p = 0.008$). While preoperative tumor markers such as CEA and CA19-9 were similar (both p value >0.10), patients with PI/MF + PI ICC tumors (27.9%; $n = 24$) were more likely to have received neoadjuvant chemotherapy compared with MF/IG patients (6.8%; $n = 53$) [$p < 0.001$]. While the overwhelming majority of patients with PI/MF + PI tumors underwent a major hepatectomy ($n = 134$, 94.4%), only approximately one-half of patients with MF/IG tumors ($n = 512$, 54.4%) had a major resection ($p < 0.001$). Lymphadenectomy was also more often performed among patients with PI/MF + PI (72.5%) versus MF/IG (40.7%) tumors ($p < 0.001$).

On final pathology, tumor size and number were comparable among patients with PI/MF + PI versus MF/IG tumors, as was the incidence of poor/undifferentiated ICC tumors (Table 1). In contrast, compared with MF/IG patients, PI/MF + PI tumors were more likely to be associated with major vascular invasion (PI/MF + PI 26.8% vs. MF/IG 9.5%), as well as lymphovascular (PI/MF + PI 46.1% vs. MF/IG 28.8%) and perineural invasion (PI/MF + PI 37.7% vs. MF/IG 17.9%) [all $p < 0.001$]. In addition, patients with PI/MF + PI tumors were more likely to have undergone a margin positive resection (PI/MF + PI 23.4% vs. MF/IG 10.8%; $p < 0.001$). PI/MF + PI patients also had a higher incidence of harboring metastatic lymph node disease (PI/MF + PI 59.2% vs. MF/IG 34.7%; $p < 0.001$).

Using the 8th edition of the AJCC staging system, PI/MF + PI patients had more advanced T categories (T2/T3/T4, PI/MF + PI 77.5% vs. MF/IG 51.4%; $p < 0.001$), as well as N status (N1, PI/MF + PI 77.2% vs. MF/IG:58.5%; $p = 0.003$). Accordingly, 95.0% of PI/MF + PI patients were staged as II/IIIa/IIIb versus 86.0% of MF/IG patients ($p = 0.017$).

Univariable and Multivariable Survival Analyses

Within a median follow-up of 1.7 years (IQR 0.91–3.46), 537 (49.6%) patients died; 3- and 5-year overall survival (OS) was 51.9% (95% confidence interval [CI] 48.6–55.3) and 39.5% (95% CI 35.7–43.3), respectively. Several variables were associated with OS on univariable analysis, including tumor markers (CEA and CA 19–9), type of surgery, margin status, invasion of adjacent organs, tumor size and number, tumor differentiation, major vascular invasion, lymphovascular invasion, perineural invasion, nodal status, and AJCC 8th edition staging (Tables 2, 3). In addition, patients with an MF/IG ICC had a 5-year OS of 41.8% (95% CI 37.7–45.9), which was markedly better than the 25.5% (95% CI 17.3–34.4) among patients with a PI/MF + PI tumor ($p < 0.001$) [Fig. 1].

On multivariable analysis, tumor size (>5 cm; hazard ratio [HR] 1.75, 95% CI 1.44–2.13), invasion of adjacent organs (HR 1.75, 95% CI 1.28–2.38), and metastatic nodal status (HR 2.42, 95% CI 1.84–3.18) [all $p < 0.001$] remained strongly associated with OS (Table 4). In addition, positive margin status (HR 1.38, 95% CI 1.06–1.79),

TABLE 1 Baseline characteristics ($n = 1083$)

Variables	ICC	MF/IG	PI/MF + PI	p Value
No. of patients	1083	941	142	
Sex				0.88
Female	466 (43.1)	404 (42.9)	62 (43.7)	
Male	617 (56.9)	537 (57.1)	80 (56.3)	
Age, years [median (IQR)]	60 (51–69)	59 (51–68)	63 (56–71)	0.008
ASA score				0.008
1–2	614 (56.7)	548 (58.2)	66 (46.5)	
3–4	469 (43.3)	393 (41.8)	76 (53.5)	
Underlying liver disease				<0.001
Cirrhosis	117 (10.8)	112 (11.9)	5 (3.5)	
Chronic HBV infection	204 (18.8)	196 (20.8)	8 (5.6)	
Chronic HCV infection	31 (2.9)	21 (2.2)	10 (7.1)	
None	731 (67.9)	612 (65.1)	119 (83.8)	
Neoadjuvant chemotherapy				<0.001
No	783 (91.1)	721 (93.2)	62 (72.1)	
Yes	77 (8.9)	53 (6.8)	24 (27.9)	
NA	223	167	56	
CA19–9, U/mL [median (IQR)]	47 (17–190)	45 (16–174)	94 (26–494)	0.12
CEA, ng/mL [median (IQR)]	2.4 (1.4–4.3)	2.4 (1.4–4.2)	2.6 (1.4–5.5)	0.72
Type of surgery				<0.001
Wedge resection	169 (15.6)	169 (18.0)	0 (0)	
Minor hepatectomy	268 (24.7)	260 (27.6)	8 (5.6)	
Major hepatectomy	646 (59.7)	512 (54.4)	134 (94.4)	
Margins				<0.001
Negative	945 (87.6)	837 (89.2)	108 (76.6)	
Positive	134 (12.4)	101 (10.8)	33 (23.4)	
NA	4	3	1	
Liver capsule involvement				0.25
No	877 (80.9)	767 (81.5)	110 (77.5)	
Yes	206 (19.1)	174 (18.5)	32 (22.5)	
Invasion of adjacent organs				<0.001
No	1017 (93.9)	901 (95.7)	116 (81.7)	
Yes	66 (6.1)	40 (4.3)	26 (18.3)	
Tumor size, cm				0.06
≤5	434 (40.1)	367 (39.0)	67 (47.2)	
>5	649 (59.9)	574 (61.0)	75 (52.8)	
Lesion				0.12
Unifocal	890 (82.2)	780 (82.9)	110 (77.5)	
Multifocal	193 (17.8)	161 (17.1)	32 (22.5)	
Grade				0.22
Well–moderate	845 (83.0)	742 (83.6)	103 (79.2)	
Poor–undifferentiated	173 (17.0)	146 (16.4)	27 (20.8)	
NA	65	53	12	
Major vascular invasion				<0.001
Not present	956 (88.3)	852 (90.5)	104 (73.2)	
Present	127 (11.7)	89 (9.5)	38 (26.8)	
Lymphovascular invasion				<0.001
Not present	736 (68.9)	660 (71.2)	76 (53.9)	

TABLE 1 continued

Variables	ICC	MF/IG	PI/MF + PI	*p* Value
Present	332 (31.1)	267 (28.8)	65 (46.1)	
NA	15	14	1	
Perineural invasion				<0.001
Not present	787 (79.5)	706 (82.1)	81 (62.3)	
Present	203 (20.5)	154 (17.9)	49 (37.7)	
NA	96	81	12	
Lymphadenectomy				<0.001
Not performed	597 (55.1)	558 (59.3)	39 (27.5)	
Performed	486 (44.9)	383 (40.7)	103 (72.5)	
Pathological nodal status[a]				<0.001
Negative	292 (60.1)	250 (65.3)	42 (40.8)	
Positive	194 (39.9)	133 (34.7)	61 (59.2)	
AJCC 8th edition N categories[b]				0.003
N0	114 (36.7)	96 (41.5)	18 (22.7)	
N1	194 (63.3)	133 (58.5)	61 (77.2)	
AJCC 8th edition T categories				<0.001
T1a	238 (21.9)	223 (23.7)	15 (10.6)	
T1b	252 (23.3)	235 (24.9)	17 (11.9)	
T2	363 (33.5)	291 (30.9)	72 (50.7)	
T3	164 (15.1)	152 (16.2)	12 (8.5)	
T4	66 (6.1)	40 (4.3)	26 (18.3)	
AJCC 8th edition stages[b]				0.017
Ia	15 (4.9)	15 (6.6)	0 (0)	
Ib	21 (6.8)	17 (7.4)	4 (5.0)	
II	47 (15.3)	37 (16.2)	10 (12.7)	
IIIa	26 (8.4)	23 (10.0)	3 (3.8)	
IIIb	199 (64.6)	137 (59.8)	62 (78.5)	

Data are expressed as *n* (%) unless otherwise specified

NA not available, *ICC* intrahepatic cholangiocarcinoma, *MF* mass forming, *IG* intraductal growth, *PI* periductal infiltrating, *IQR* interquartile range, *ASA* American Society of Anesthesiologists, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *CA* cancer antigen, *CEA* carcinoembryonic antigen, *AJCC* American Joint Committee on Cancer

[a] Patients who underwent lymphadenectomy ($N = 486$)

[b] Patients who had at least six lymph nodes harvested ($N = 308$)

multifocal ICC (HR 1.38, 95% CI 1.11–1.72), poor/undifferentiated tumor grade (HR 1.60, 95% CI 1.28–2.01), and perineural invasion (HR 1.28, 95% CI 1.01–1.62) [all $p < 0.05$] were also associated with a poor prognosis. Of note, after controlling for these competing risk factors, morphological subtype remained associated with OS as patients with a PI/MF + PI ICC had an approximately 40% higher hazard of death compared with patients who had MF/IG ICC (HR 1.42, 95% CI 1.11–1.82) [$p = 0.006$].

Prognosis of Patients and Morphological Types

Given the baseline differences between the MF/IG and PI/MF + PI groups, a propensity score-matching analysis was then performed to minimize potential confounding. Patients were matched based on age, ASA score, underlying liver disease, neoadjuvant chemotherapy, type of surgery, margin status, invasion of adjacent organs, tumor size and number, tumor differentiation, vascular invasion, lymphovascular invasion, perineural invasion, lymph node status, and AJCC 8th edition T categories.

After the propensity score matching, 95 patients in the PI/MF + PI group and 95 patients in the MF/IG group had comparable characteristics and were subsequently analyzed (electronic supplementary Table S1) [all $p > 0.1$]. In the propensity score-matched analysis, individuals with MF/IG ICC still had a more favorable prognosis compared with patients who had PI/MF + PI tumors (5-year OS: MF/IG 35.7%, 95% CI 24.0–47.6 vs. PI/MF + PI 26.2%, 95% CI 16.4–37.1) [$p = 0.03$].

TABLE 2 Univariate survival analysis ($n = 1083$)

Variables	$N = 1083$ [n (%)]	5-year OS (%)	95% CI	p Value
Sex				
Female	66 (43.1)	37.7	32.7–42.7	0.28
Male	617 (56.9)	41.9	36.1–47.6	
Age, years				0.63
≤65	675 (62.3)	39.4	34.7–44.0	
>65	408 (37.7)	39.5	33.1–45.8	
ASA score				0.09
1–2	614 (56.7)	40.9	35.6–46.0	
3–4	469 (43.3)	37.4	31.9–42.9	
Underlying liver disease				<0.001
Cirrhosis	117 (10.8)	112 (11.9%)	5 (3.5%)	
Chronic HBV infection	204 (18.8)	196 (20.8%)	8 (5.6%)	
Chronic HCV infection	31 (2.9)	21 (2.2%)	10 (7.1%)	
None	731 (67.9)	612 (65.1%)	119 (83.8%)	
Morphological types				<0.001
MF/IG	941 (86.9)	41.8	37.7–45.9	
PI/MF + PI	142 (13.1)	25.5	17.3–34.4	
Neoadjuvant chemotherapy				0.69
No	783 (91.1)	44.0	39.3–48.6	
Yes	77 (8.9)	42.5	26.8–57.3	
CA19-9, U/mL				<0.001
≤50	400 (51.4)	50.7	44.2–56.9	
>50	379 (48.5)	31.5	25.6–37.5	
CEA, ng/mL				<0.001
≤10	592 (89.9)	42.9	37.5–48.2	
>10	66 (10.1)	4.2	0.4–16.4	
Type of surgery				0.011
Wedge resection	169 (15.6)	40.2	29.4–50.7	
Minor hepatectomy	268 (24.7)	49.1	40.8–56.8	
Major hepatectomy	646 (59.7)	37.8	32.8–42.8	
Margins				<0.001
Negative	945 (87.6)	40.9	36.9–44.9	
Positive	134 (12.4)	29.6	20.1–39.6	
Liver capsule involvement				
No	877 (80.9)	39.7	35.4–43.9	
Yes	206 (19.1)	38.5	30.7–46.3	0.47
Invasion of adjacent organs				<0.001
No	1017 (93.9)	43.3	39.1–47.5	
Yes	66 (6.1)	14.7	6.4–26.5	
Tumor size, cm				<0.001
≤5	434 (40.1)	51.9	45.9–57.7	
>5	649 (59.9)	30.7	26.1–35.5	
Lesion				<0.001
Unifocal	890 (82.2)	43.3	39.0–47.5	
Multifocal	193 (17.8)	22.9	16.0–30.6	
Grade				<0.001
Well–moderate	845 (83.0)	42.9	38.6–47.2	
Poor–undifferentiated	173 (17.0)	22.3	14.9–30.7	

TABLE 2 continued

Variables	$N = 1083$ [n (%)]	5-year OS (%)	95% CI	p Value
Major vascular invasion				<0.001
Not present	956 (88.3)	41.6	37.5–45.6	
Present	127 (11.7)	26.4	17.4–36.2	
Lymphovascular invasion				0.004
Not present	736 (68.9)	43.0	38.5–47.4	
Present	332 (31.1)	31.6	26.7–38.7	
Perineural invasion				0.001
Not present	787 (79.5)	42.7	38.4–46.9	
Present	203 (20.5)	22.1	13.7–31.8	
Lymphadenectomy				0.07
Not performed	597 (55.1)	43.9	38.9–48.8	
Performed	486 (44.9)	33.4	27.7–39.1	
Pathological nodal status[a]				<0.001
Negative	292 (60.1)	44.3	36.6–51.7	
Positive	194 (39.9)	15.7	8.9–24.1	
AJCC 8th edition N categories				
N0	114 (36.7)	54.5	40.9–66.2	<0.001
N1	194 (63.3)	15.6	8.9–23.9	
AJCC 8th edition T categories				<0.001
T1a	238 (21.9)	60.9	52.7–68.2	
T1b	252 (23.3)	33.9	26.0–41.8	
T2	363 (33.5)	29.9	23.6–36.5	
T3	164 (15.1)	45.8	36.6–54.6	
T4	66 (6.1)	14.7	6.4–26.5	
AJCC 8th edition stages[b]				<0.001
Ia	15 (4.9)	90.9	50.8–98.7	
Ib	21 (6.8)	51.9	23.4–74.3	
II	47 (15.3)	48.0	27.7–65.7	
IIIa	26 (8.4)	42.5	13.4–69.4	
IIIb	199 (64.6)	16.6	9.8–25.1	

NA not available, *OS* overall survival, *CI* confidence interval, *MF* mass forming, *IG* intraductal growth, *PI* periductal infiltrating, *ASA* American Society of Anesthesiologists, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *CA* cancer antigen, *CEA* carcinoembryonic antigen, *AJCC* American Joint Committee on Cancer

[a] Patients who underwent lymphadenectomy ($N = 486$)

[b] Patients who had at least six lymph nodes harvested ($N = 308$)

American Joint Committee on Cancer 8th edition T categories and Morphological Types

Patients were then stratified according to the AJCC 8th edition T categories, as well as morphologic subtypes (Tables 5, 6). A total of 749 (69.2%) patients were in the MF/IG group and in T1a–T1b–T2 stages compared with only 104 (9.6%) patients in the PI/MF + PI group and T1a–T1b–T2 stages. Furthermore, 192 (17.7%) patients were in the MF/IG group and in T3–T4 stages, while 38 (3.5%) patients were in the PI/MF + PI group and in T3–T4 stages. Of note, even among the T1a–T1b–T2 categories, patients with MF/IG morphology had a better 5-year OS of 41.6% (95% CI 36.9–46.3) versus 32.0% (95% CI 21.6–42.9) for patients with a PI/MF + PI ICC ($p < 0.001$). Similarly, among patients categorized as T3–T4, 5-year OS following resection of an MF/IG ICC tumor was 42.5% (95% CI 34.1–50.7) compared with only 5.6% (95% CI 0.5–20.6; $p < 0.001$) for PI/MF + PI ICC tumors (Fig. 2). Moreover, compared with T1a–T1b–T2 MF/IG tumors, T1a–T1b–T2 PI/MF + PI (HR 1.47, 95% CI 1.11–1.94) and T3–T4 PI/MF + PI (HR 3.59, 95% CI 2.46–5.23) lesions were associated with an increased risk of death. In contrast, patients with a T3-T4 MF/IG tumor had a comparable risk of death

TABLE 3 Comparison between morphological types—Kaplan–Meier analysis

	$N = 1083$ [n (%)]	5-year OS (%)	95% CI	p Value
Morphological types				<0.001
MF/IG	941 (86.9)	41.8	37.7–45.9	
PI/MF + PI	142 (13.1)	25.5	17.3–34.4	
Morphological types—after PS[a]	$N = 190$			0.034
MF/IG	95 (50.0)	35.7	24.0–47.6	
PI/MF + PI	95 (50.0)	26.2	16.4–37.1	

OS overall survival, *CI* confidence interval, *MF* mass forming, *IG* intraductal growth, *PI* periductal infiltrating

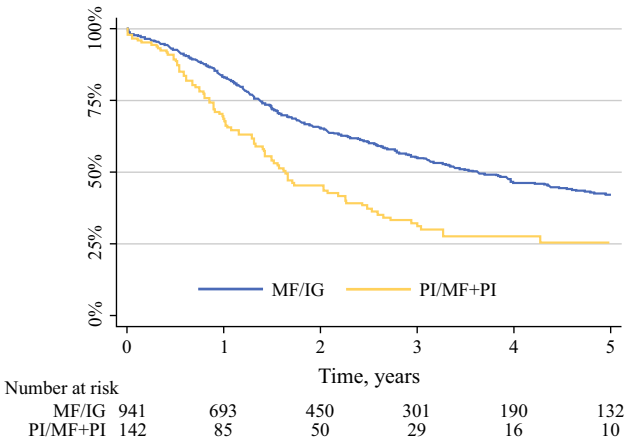

FIG. 1 Kaplan–Meier overall survival curves stratified by morphological type classification. *MF* mass forming, *IG* intraductal growth, *PI* periductal infiltrating

versus patients who had a T1a–T1b–T2 MF/IG lesion (HR 1.01, 95% CI 0.79–1.28) [$p = 0.95$].

DISCUSSION

Similar to other solid malignancies, there has been significant interest in identifying clinicopathological factors associated with survival among patients undergoing curative-intent surgery for ICC. To this end, several groups have proposed various staging and prognostic schemes to stratify ICC patients with regard to prognosis.[2,26] For example, Hyder et al. reported a nomogram that included six factors, including age, tumor size, number of lesions, nodal status, vascular invasion, and the presence of cirrhosis.[26] While the nomogram performed reasonably well, the overall accuracy was only moderate, with a C-statistic of 0.706. Such data suggest that other factors may be important in stratifying patient prognosis following resection of ICC. One such possible factor may be tumor morphology, which was first classified by the Liver Cancer Study of Japan.[20] To date, most studies on ICC have failed to consider, or even report, the morphologic subtype of ICC tumors included in the analytic cohort.[2,7,9,12–17] The current study is important because we were able to examine the impact of morphologic ICC subtype in a large, multicenter cohort of over 1000 patients undergoing surgery for ICC at one of 14 major hepatobiliary centers in the US, Europe, Australia, and Asia. Specifically, we noted that patients with an MF/IG ICC had a much more favorable prognosis compared with patients who had PI/MF + PI tumors. In particular, PI/MF + PI tumors were associated with many more aggressive features than MF/IG lesions. Interestingly, even after controlling for these competing risk factors, morphologic subtype remained associated with long-term survival. Moreover, when patients were stratified by the AJCC 8th edition staging, ICC tumor morphology was still associated with prognosis within T-category subgroups (Tables 5, 6).

Similar to previous reports, clinical variables associated with survival included lymph node status, tumor size and number, positive margin status, tumor grade, and lymphovascular and perineural invasion.[6,27] More importantly, ICC morphologic type was also strongly associated with OS. Specifically, patients with an MF/IG ICC had a 5-year OS of 41.8% versus 25.5% for patients with a PI/MF + PI tumor ($p < 0.001$). Of note, after propensity score matching to control for potential confounding, MF/IG patients still were noted to have a better OS compared with patients who had PI/MF +PI tumors (35.7% vs. 26.2%, respectively). These data were consistent with Shimada et al., who reported that patients with MF ICC tumors had a more favorable prognosis versus the MF + PI subtype.[21] Furthermore, in a separate small study on 52 patients undergoing curative-intent surgery for ICC, Guglielmi et al. reported that patients with MF tumors (50 months) had a markedly longer median survival compared with either the MF/PI subtype (19 months) or the pure PI subtype (15 months).[28] In addition, in the current study, the MF + PI ICC subtype was associated with more aggressive tumor characteristics, which was consistent with the study by Shimada et al., which reported MF + PI ICC

TABLE 4 Multivariable survival analysis—Cox's model

Variables	HR	95% CI	*p* Value
Invasion of adjacent organs			<0.001
No	–	–	
Yes	1.75	1.28–2.38	
Margins			0.015
Negative	–	–	
Positive	1.38	1.06–1.79	
Tumor size, cm			<0.001
≤5	–	–	
>5	1.75	1.44–2.13	
Lesion			0.003
Unifocal	–	–	
Multifocal	1.38	1.11–1.72	
Grade			<0.001
Well–moderate	–	–	
Poor–undifferentiated	1.60	1.28–2.01	
Perineural invasion			0.043
Not present	–	–	
Present	1.28	1.01–1.62	
Pathological nodal status[a]			<0.001
Negative	–	–	
Positive	2.42	1.84–3.18	
Not harvested	1.59	1.27–2.02	
Morphological types			0.006
MF/IG	–	–	
PI/MF + PI	1.42	1.11–1.82	

HR hazard ratio, *CI* confidence interval, *MF* mass forming, *IG* intraductal growth, *PI* periductal infiltrating

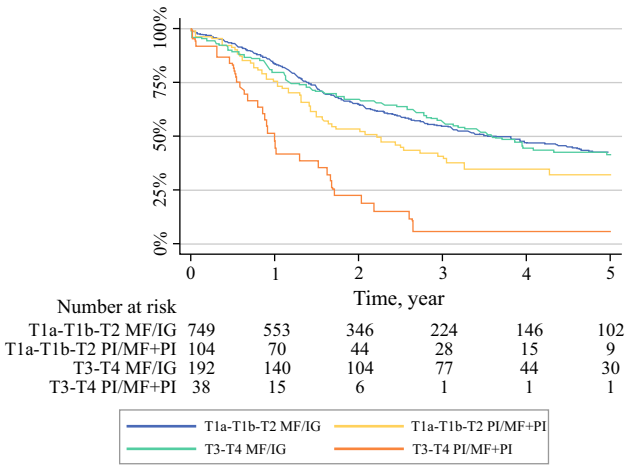

FIG. 2 Kaplan–Meier overall survival curves stratified by the AJCC 8th edition T-category staging and morphological type classification. *AJCC* American Joint Committee on Cancer, *MF* mass forming, *IG* intraductal growth, *PI* periductal infiltrating

macroscopic tumor types to be associated with increased risk of jaundice, bile duct invasion, portal vein invasion, lymph node metastasis, and R1 margins.[21]

To further evaluate the prognostic effect of gross tumor morphology, prognosis was stratified by AJCC 8th edition T categories by morphological subtype. Among T1a–T1b–T2 patients (i.e. solitary tumor measuring ≤ 5 cm [T1a]; solitary tumor >5cm [T1b]; solitary tumor with intrahepatic vascular invasion or multiple tumors, with or without vascular invasion [T2]), patients with MF/IG ICC had a 5-year OS of 41.6 versus 32.0% for patients with PI/MF + PI tumors ($p < 0.001$). A similar difference in survival based on ICC morphologic subtype was noted among patients with T3–T4 tumors. Interestingly, T3–T4 MF/IG patients had a similar risk of death as patients with T1a–T1b–T2 MF/IG tumors ($p = 0.95$). Similarly, in a recent paper from our group comparing the AJCC 7th versus 8th edition staging systems for ICC, 8th edition T3 patients paradoxically had a better 5-year OS than either T1 or T2 patients.[29] These data, in conjunction with data from the current study, suggest that factors other than those currently included in the AJCC staging manual are needed to improve prognostication of survival among patients with ICC.

TABLE 5 Multivariable survival analysis—Cox's model with AJCC 8th edition T categories

Variables	HR	95% CI	*p* Value
AJCC 8th edition T categories			
T1a	–	–	–
T1b	2.01	1.49–2.70	<0.001
T2	2.27	1.71–3.00	<0.001
T3	1.60	1.15–2.23	0.005
T4	3.94	2.71–5.75	<0.001
Morphological types			0.003
MF/IG	–	–	
PI/MF + PI	1.45	1.14–1.84	

AJCC American Joint Committee on Cancer, *HR* hazard ratio, *CI* confidence interval, *MF* mass forming, *IG* intraductal growth, *PI* periductal infiltrating

TABLE 6 AJCC 8th edition and morphological type

	N = 1083 [*n* (%)]	5-year OS (%)	95% CI	*p* Value
AJCC 8th edition T categories				<0.001
T1a–T1b–T2 and MF/IG	749 (69.2)	41.6	36.9–46.3	
T1a–T1b-T2 and PI/MF + PI	104 (9.6)	32.0	21.6–42.9	
T3–T4 and MF/IG	192 (17.7)	42.5	34.1–50.7	
T3–T4 and PI/MF + PI	38 (3.5)	5.6	0.5–20.6	
	N = 1083 [*n* (%)]	HR	95% CI	*p* Value
AJCC 8th edition T categories				
T1a–T1b–T2 and MF/IG	749 (69.2)	–	–	–
T1a–T1b–T2 and PI/MF + PI	104 (9.6)	1.47	1.11–1.94	0.007
T3–T4 and MF/IG	192 (17.7)	1.01	0.79–1.28	0.95
T3–T4 and PI/MF + PI	38 (3.5)	3.59	2.46–5.23	<0.001

AJCC American Joint Committee on Cancer, *OS* overall survival, *HR* hazard ratio, *CI* confidence interval, *MF* mass forming, *IG* intraductal growth, *PI* periductal infiltrating

The current paper had several limitations that should be considered. The retrospective nature of the study may have resulted in selection bias; however, such confounding was unlikely to impact the evaluation of the prognostic effect of the morphological status. The multi-institutional nature of the study likely also caused some heterogeneity in ICC treatment approach. Finally, the pathological evaluation of ICC was conducted separately in each center, resulting in some heterogeneity in the interpretation of the pathological ICC characteristics. However, including multiple tertiary referral hepato-pancreatico-biliary (HPB) centers allowed for a large sample size and a more 'real-world' cohort.

CONCLUSION

Among patients undergoing curative-intent resection of ICC, morphologic subtype was associated with long-term outcome. In particular, patients with PI or MF + PI ICC had an approximately 45% increased risk of death compared with patients who had an MF or IG ICC. Interestingly, T3–T4 MF/IG patients had a similar risk of death as T1a–T1b–T2 MF/IG patients. Collectively, these data suggest that further refinements of staging, such as including tumor morphology, may be needed to better define the prognosis of patients with ICC.

DISCLOSURE The authors have no personal conflicts of interest to declare.

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